Hypertension Pharmacology

Introduction

Like we did with hypertension pathogenesis, we're going to keep this focused on the mechanisms and give a teaser of clinical practice. We'll do this in a way you won't find anywhere else. We're going to link antihypertensives based on the MAP equation, showing you how categorizing them in that way can align with your understanding of the mechanisms of hypertension. That isn't how we're going to organize them when you hit clinicals, though. In the Clinical Sciences, we'll talk about comorbid conditions, organize medications by potency and relative blood pressure currency, set therapeutic goals, and choose medications based on the extra beneficial side effects that come with them.

Now, we want to break the anxiety that comes with opening a pharmacology textbook and being confronted with 17 unrelated drug classes, or worse, lumping medications together that have no business being lumped together. The thing is, pharmacology textbooks organize hypertension medications based on how pharmacologists catalog drugs. By the end of this lesson, you will not have mastered these medications—we're going to talk about them in various clinical contexts throughout the course—but you will have a clinical organization and a better sense of how medications are actually used in practice.

In this lesson, you will be introduced to drug classes organized according to the MAP equation and then get a gentle orientation to choosing the right medication for the right disease. Don't go chasing down explanations you don't understand. Don't start making flashcards as if this were the definitive information. This lesson is merely a preview, an organization of a massive subject that has implications across all of cardiology, beyond just hypertension pharmacology, and deep into clinical. As you progress through our Basic Sciences curriculum, you will encounter these drug classes again. There, with specialization and narrow focus, we will go into the details. This lesson has tremendous clinical perspective translated into an advanced organizer you are familiar with—the MAP equation. We want you to start this journey with the end in mind. But the road only starts here, not ends.

A Little Rant From Dr. Williams

You're doing it wrong. You're all doing it wrong! Not you, the learner, but every basic sciences educator who lacks clinical perspective. What they're doing is not inaccurate by the science we have. But it is woefully inadequate for what you need when someone in front of you has hypertension. This rant may mean nothing to you, yet. But, you'll get the gist even if you haven't studied these things before.

Gripe 1: *Calcium-channel blocker is not a drug class.*

"Verapamil, diltiazem, and the dihydropyridine family (amlodipine, felodipine, isradipine, nicardipine, nifedipine, nisoldipine, and nitrendipine [withdrawn in the USA]) are all equally effective in lowering blood pressure . . ."[1]

Let's see here, you little quote from Katzung . . . let's just do a little testy test in real life.

If someone had atrial fibrillation with rapid ventricular response, and bolus doses weren't working to control the rate, I would admit that patient to my floor (a cardiac floor that enabled my nursing staff to manage non-titratable drips outside of an ICU) and put them on an infusion of diltiazem. Diltiazem is a non-dihydropyridine **calcium-channel blocker**.

If someone had a hypertensive emergency—very high blood pressure with signs of end-organ damage—I would place that person into the intensive care unit on an infusion of nicardipine. The nurse there would titrate to effect—reduce the MAP by 25% in the first 6 hours, administer oral medications, and down-titrate the drip as the nurse is able. Nicardipine is a dihydropyridine **calcium-channel blocker**.

Both are infused through an IV, and both are calcium-channel blockers. Diltiazem did not cause hypotension because it is a **rate-control agent**. Nicardipine did not cause bradycardia because it an **antihypertensive agent**. I do not care whether medical science believes that it's "the same calcium channel" in your physiology studies. I do not care that there have been no studies that compare the two to show one is different. If it is that important, someone should go ahead and do it already. But guess what. They are NOT equally effective. Because they have drastically different effects in humans *in vivo*, they are obviously different drug classes. It might be the same type of channel, but they certainly affect different cells' channels. Yet, somehow, in every textbook and even treatment guidelines, "calcium-channel blockers" is the one drug class. Amlodipine is one of the most potent (chronic) oral antihypertensives and does nothing to control heart rate. Extended-release verapamil is a really good rate-control agent but barely does anything to blood pressure.

Both are calcium-channel blockers. **They do not belong together in any way.**

There are non-dihydropyridine calcium-channel blockers (NDHP-CCB), and there are dihydropyridine calcium-channel blockers (DHP-CCB). When someone uses "calcium-channel blocker" without the (N)DHP prefix (which is essentially all the time), you should be able to infer from the context which one they mean.

For example: Calcium-channel blockers are excellent rate-control agents for AFib. (NHDP-CCB)
For example: Use calcium-channel blockers for blood pressure control. (DHP-CCB)

Gripe 2: α_1-*Blockers are not antihypertensives.*

The -zosins, drugs like doxazosin and terazosin, are used to treat benign prostatic hyperplasia. Their side effect is orthostatic hypotension. Pharma has gone to great lengths to synthesize terazosin, the α_1-blocker with the **least systemic effects**. The goal is to create a drug that treats BPH **without reducing systemic blood pressure**. Yes, the antagonism of α_1 receptors induces vasodilation and reduces blood pressure. But it is an unintended side effect that pharma is actively trying to eliminate. Just because "it's α_1" in some nebulous way doesn't make it appropriate for the treatment of hypertension.

However, α_1 blockade is not unrelated to hypertension management. When dealing with pheochromocytoma (an endocrine disease of excess epinephrine production), α_1-blockers other than those used to treat BPH are used. Some β-blockers are also α_1-blockers. It's just that the notion that α blockade in general can be applied to HTN in general is false.

And lastly, the final example. Gripe 3: β-*Blocker is not a drug class.*

Nonselective β-blockers, like propranolol and nadolol, are used in esophageal varices and stage fright. Neither has any business near heart disease. These can induce asthma because they block β_1 and β_2. And yet there they are, littered throughout review material and even textbooks, used the wrong way, presented to students in cardiovascular disease. **Timolol** is used as an eye drop for glaucoma because administering it systemically causes such terrible systemic side effects. Did some manufacturer make an oral form of timolol? Yes. So when you search in drug databases online, there's oral timolol!

β_1-Selective β-blockers, such as **metoprolol**, are not antihypertensives but rather rate-control agents. Metoprolol is used to control the heart rate of tachycardic arrhythmias, such as atrial fibrillation. It is also indicated in the treatment of both coronary artery disease (CAD) and heart failure with reduced ejection fraction (CHF). Choose metoprolol where there is an indication for β blockade (CAD, CHF) and either rate control is desired (comorbid atrial fibrillation, for example) or blood pressure reduction is not needed.

β_1-α_1 β-Blockers, such as **carvedilol**, are chosen when β-blockade is required for another diagnosis (such as CAD or CHF), and rate control is not a concern or additional blood pressure reduction is desired. Here, the α_1 inhibition is desired and does reduce blood pressure.

Oh, hey, guess what? Both JNC-8 and ACC/AHA implied that **β-blockers are not antihypertensives** when they included them only as a **fourth choice** for oral medications to manage hypertension.

So with that real-world perspective, allow me to step off that soapbox and return the text to the voice you are accustomed to. When you see this content presented differently elsewhere, ignore it. When your superior insists you use any method other than the one we provide, listen to them, they are your superior. But then send them this document from your ex's email account, and ask them to read the first two pages. But, like, 2 weeks later so they don't know it was from you.

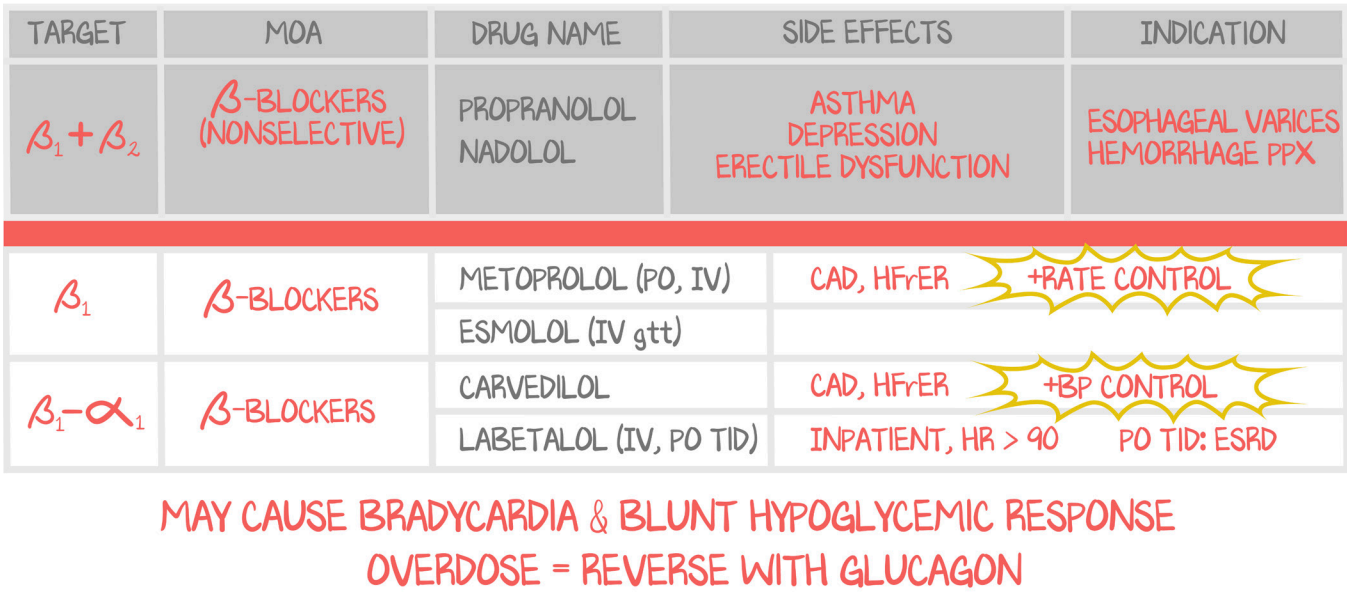


Figure 6.1: β-Blockers Do Not Treat Hypertension

MAP Equation on Drugs

We're going to expose you to information that we aren't going into detail on. Things like the Katrina switch, macula densa, JG apparatus, etc. What you get here is a preview of what is to come. When you come back after Renal, you will understand why we did it this way. Cardiology is the first module we intend you to do, so we assume that you have no knowledge of any other organ system. Thus, explanations here are high-level, without detail, and may seem obnoxiously vague. Not sorry. You're welcome.

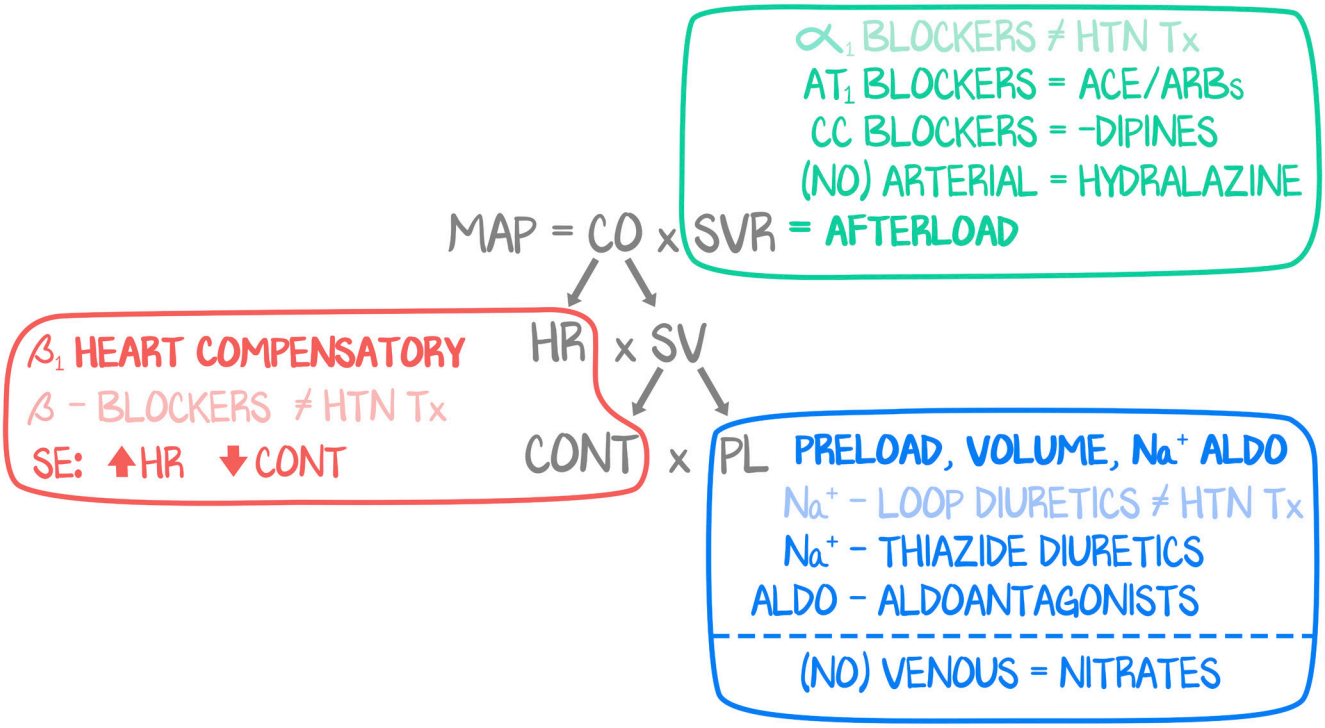


Figure 6.2: MAP Equation on Drugs
Using the familiar MAP equation, we are cataloging the classes and mechanisms of agents that can be used to treat hypertension. Agents that influence the heart—decrease heart rate or contractility—could theoretically be used to treat hypertension. Yet they are not. β_1-Receptor activation is at the heart of compensatory mechanisms for acutely falling blood pressure and, as you will see in the Structure and Function island, the pathogenic source of heart failure. There are plenty of good reasons to block β1 receptors, but they play no role in hypertension. Instead, most often targeted are systemic vascular resistance—AT_1 blockade by ACE/ARBs, calcium channel blockade by the dihydropyridine calcium-channel blockers (-dipines), and nitric oxide-induced vasodilation with hydralazine—and preload—sodium reduction via thiazide diuretics, aldosterone antagonism, and nitric oxide-induced venodilation by nitrates. None of this should make sense yet. By the end of the lesson, it should.

Systemic vascular resistance is **afterload**. Vasoconstriction leads to increased afterload and higher blood pressure. Vasodilation leads to decreased afterload and lower blood pressure. The medications that work on afterload are those that block angiotensin 2 from "tensing the angios," those that block norepi and epi from activating α_1 receptors (see Dr. Williams' rant), those that block L-type calcium channels on the smooth muscle of the vasculature, and those that act through arterial nitric oxide.

Volume is **preload**. Volume is sodium. Where sodium goes, water follows. Drugs that prevent the reabsorption of sodium in the renal tubule lead to the loss of volume. These are thiazide diuretics and aldosterone antagonists (and indirectly ACE/ARBs). Related to this system are the loop diuretics.

Heart rate and contractility are the **β_1 adrenergic receptor system**. Agents that target heart rate and contractility are not agents used for hypertension. They can aid in blood pressure reduction, but treating hypertension is not their intended purpose. They are highly valuable agents for treating heart disease (CAD and CHF) and controlling heart rate, but not plain hypertension. These are the β-blockers.

Oops. Preload is also the veins. Venodilators, such as nitrates, reduce preload, too, but only temporarily, and they don't bother themselves with sodium. This is a new concept added to the MAP equation, and it doesn't fit so nicely with our *volume = Na = aldo* concept. And, as we will see, the whole system cannot be so neat and tidy. There are others that weasel their way in there. But we'll show you that they actually don't matter, that they are old, or that you shouldn't use them.

Afterload Reducers = Arterial Vasodilators

ACE inhibitors and **angiotensin receptor blockers** (which together we call ACE/ARBs) block the angiotensin 2 effect on blood vessels. Their side effects and consequences are discussed under "Preload Reducers" below. To be clear, medications that inhibit angiotensin 2 double-dip—vasodilation and reduced preload.

Calcium-channel blockers that are antihypertensives, the dihydropyridine CCBs like amlodipine (PO), nifedipine (PO), and nicardipine (IV), block voltage-gated calcium channels in the vascular smooth muscle of blood vessels. They cause arterial vasodilation. Because they do that, more blood gets to capillary beds. More blood in without a means to get more blood out can lead to peripheral edema (a potential side effect of these medications). They are also potent anti-anginals, so they are a good option for patients who are maximized on their coronary artery disease medications, still require additional blood pressure control, and have angina.

Hydralazine is an arterial dilator. It works by inducing the release of nitric oxide. Nitric oxide is how the endothelial cells of the tunica intima tell the smooth muscle cells of the tunica media to relax. Hydralazine only works on arteries. It is known to cause reflex tachycardia (which goes away when on a stable dose) and will be your inpatient go-to for intravenous control of out-of-range blood pressures and slow heart rate (see labetalol below, under "Ancient, Should Not Use"). At high doses, it is known to cause drug-induced lupus. Look for anti-histone antibodies and joint/skin symptoms without any visceral involvement. Bonus if it's an older man who isn't African American (the exact opposite demographic of those at highest risk for developing actual lupus—African-American women).

TARGET	MOA	DRUG FAMILY	SIDE EFFECTS		INDICATED
AT_1	ACE:	"-PRILS"	ANGIOEDEMA DRY COUGH	↑CR ↑K TERATOGENIC	CHF, CAD CKD, DM ETC.
	ARB:	"-ARTANS"	–		
CALCIUM CHANNEL	DHP-CCB	"-DIPINES"	PERIPHERAL EDEMA	–	POTENT HTN ANTIANGINAL
(NO)	ARTERIES' DILATION	HYDRALAZINE	REFLEX TACHYCARDIA	DRUG-INDUCED LUPUS	INPATIENT IV (HR <90) CHF AS BiDil®

Figure 6.3: Drug Classes That Target Afterload

Preload Reducers

ACE (-prils)**/ARBs** (-artans) induce their primary benefit on hypertension by preventing the "tensing of the angios." They block angiotensin 2-dependent vasoconstriction and, therefore, lead to vasodilation and reduced preload. That's great. Their shared side-effect profile (ACE inhibitors have more side effects than ARBs) comes down to the kidney. Angiotensin 2 causes efferent arteriole vasoconstriction, whereas tubuloglomerular feedback prevents vasoconstriction of the afferent arteriole (you aren't supposed to understand any of that, so we chose to say it in all technical jargon). The net effect is that the efferent arteriole constricts more than the afferent arteriole, which leads to an increased glomerular filtration rate. Here's the takeaway: when you block angiotensin 2 effects with an ACE/ARB, you dilate the

efferent arteriole more than the afferent arterioles, compromising the glomerular filtration rate. But just a little. So you can expect a < 20% rise in creatinine levels. It isn't renal failure, it's just an anticipatable effect. This makes them good for diabetics with microalbuminuria and bad for CKD-4 patients. The other thing angiotensin 2 does is induce the production of aldosterone. Blocking angiotensin 2 blocks aldosterone. As we will see in a moment, blocking aldosterone can cause hyperkalemia. **Elevated creatinine** and **elevated potassium** are side effects of ACE/ARBs. They are indicated in **heart failure**, **chronic kidney disease** (other than stage 4), **diabetes**, **coronary artery disease**, etc., etc. Good drugs. ACE/ARBs are intensely teratogenic. A woman cannot get pregnant on these drugs. ACE inhibitors (but not ARBs) can cause **angioedema** and **a dry cough** because they interfere with the bradykinin pathway. Again, just a high-level overview. We're going to talk about these drugs in three islands in Cardiology, two islands in Renal, and a island in Endocrine.

Aldosterone antagonists, such as spironolactone and eplerenone, don't touch angiotensin 2 at all. They specifically block the effects of aldosterone only. Aldosterone is responsible for the insertion of channels that passively reabsorb sodium from the collecting duct. In doing so, potassium is forced into the urine to keep things electroneutral. Therefore, aldosterone has two roles. One is the reabsorption of sodium, which we are equating with volume, with preload. The second is potassium regulation. Aldosterone antagonists may provoke hyperkalemia.

Thiazide diuretics, such as hydrochlorothiazide and chlorthalidone, block sodium reabsorption in the distal convoluted tubule of the nephron. This increases distal sodium delivery to the collecting duct. The collecting duct tries, but fails, to handle the excess sodium burden. As more sodium is reabsorbed, more potassium is lost. Thiazides can cause hypokalemia. Thiazide diuretics can precipitate gout flares by preventing urate secretion and can be used to prevent calcium oxalate kidney stones. Rarely, thiazides cause pancreatitis.

Loop diuretics, like furosemide and torsemide, do affect blood pressure. You cannot simply give them intravenously and not worry about the pressure shifts. They eliminate preload. But their duration is so short that they are not effective at managing blood pressure. They are so potent that they take off too much volume too quickly. They are preload reducers. But they are NOT antihypertensives. They are used to maintain urine output in chronically failing kidneys. They are also used to manage hypervolemic states, like CHF with volume overload or ascites. They have a huge impact on sodium delivery, so they can cause hypokalemia. If they remove excess volume, they can provoke prerenal azotemia (acute kidney injury due to volume depletion). They also cause magnesium wasting.

We omit the newer medication class of neprilysin inhibitors (sacubitril) because it muddies up the diuretic aldosterone story. You'll see it in more detail in the management of heart failure.

Preload Reducers Non-Kidney Nitrates

Nitrates. Whether sublingual rapid-acting nitroglycerin, intravenous nitroprusside, or taken-as-a-pill-every-day isosorbide dinitrate (ISDN) and isosorbide mononitrate (ISMN), nitrates work on veins the way hydralazine works on arteries. Nitric oxide induces venodilation. Blood pools in capacitance veins. Preload is reduced. This doesn't do anything long term, as the preload, the volume, is still in the person, but it relaxes the heart by making it feel like there is less preload.

Nitroprusside used to be the best infused antihypertensive we had, so we tolerated the fact that it **turns into cyanide** after prolonged use. Hey, 1989, we've got newer, better drugs now. Don't use nitroprusside when you have something else.

ISDN is combined with hydralazine in the management of heart failure. ISMN is an anti-anginal. Nitrates cannot be combined with PDE5 inhibitors (sildenafil, tadalafil)—the erectile dysfunction medications—because they can cause a dangerous drop in blood pressure. A common side effect is headache.

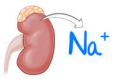
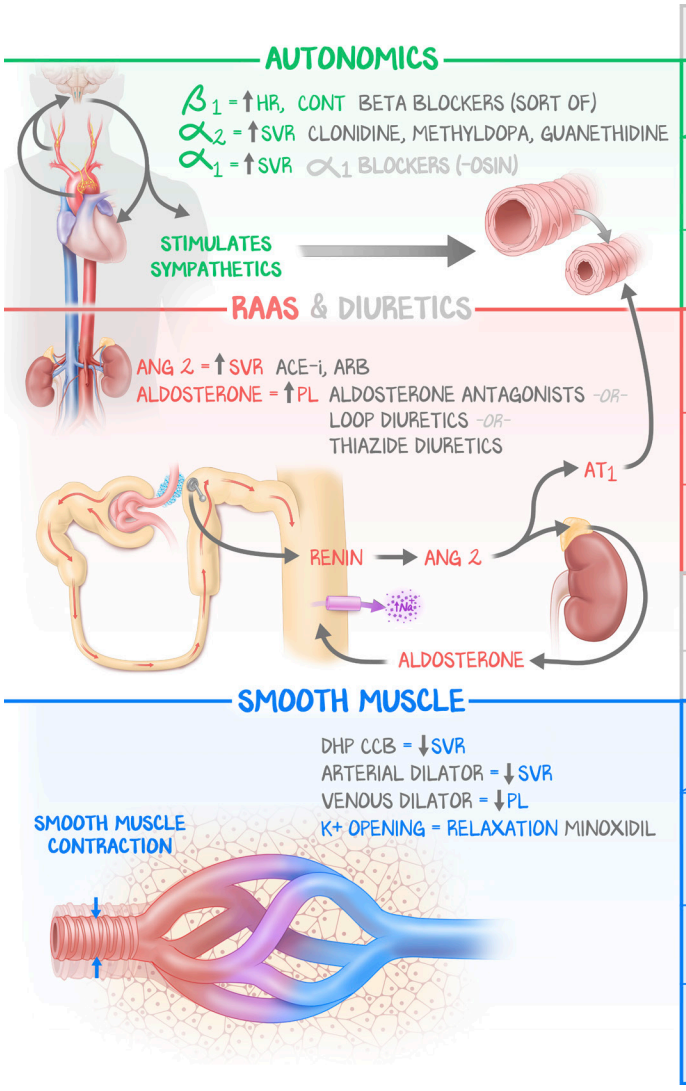
TARGET	MOA	DRUG FAMILY	SIDE EFFECTS	ALSO TREATS
	THIAZIDE DIURETICS	HYDROCHLOROTHIAZIDE (HCTZ) CHLORTHALIDONE	↓K, PANCREATITIS, HELP CaOXALATE STONES	HTN ONLY
	LOOP DIURETICS	FUROSEMIDE TORSEMIDE	↓K, ↓Mg, OTOTOXICITY ↑CR FROM ↓VOL	VOLUME OVERLOAD (CHF, ASCITES)
	ALDOSTERONE ANTAGONISTS	SPIRONOLACTONE* EPLERENONE	GYNECOMASTIA* ↑K (CAUTION CHF = ACE)	VOLUME OVERLOAD (CHF, ASCITES)
	NITRATES	ISOSORBIDE MONONITRATE	HEADACHE ↓ BP WITH PDE-5-I	HTN, CAD, ANTIANGINAL
		ISOSORBIDE DINITRATE (BiDil®)	"	CHF

Figure 6.4: Drug Classes That Target Preload

Visualizing Antihypertensives Another Way



CLASS	DRUG NAMES	EFFECT	NOTES
~~α1 BLOCKERS~~	~~TAMSULOSIN DOXAZOSIN~~	X	PBH, CAUSE ORTHOSTATICS
α2 AGONISTS	CLONIDINE METHYLDOPA	↓SVR	REBOUND HTN SLE LAST RESORT
β1 BLOCKERS	"-OLOL"	↓HR ↓CONT	BRADYCARDIA NOT FRONT LINE
ACE-i	"-PRILS"	↓SVR	COUGH ANGIODEMA ↑K+ ↑Cr
ARB	"-SARTAN"	↓SVR	↑K+ ↑Cr
ALDOSTERONE ANTAGONIST	SPIRONOLACTONE EPLERENONE	↓PL	↑K+ ↑Cr
LOOP	FUROSEMIDE	↓PL	VOLUME OVERLOAD ↓BP SIDE EFFECT
THIAZIDE	HCTZ	↓PL	↓K+
~~NON-DHP CALCIUM CHANNEL BLOCKERS~~	~~VERAPAMIL DILTIAZEM~~	X	RATE CONTROL ONLY
DHP CALCIUM CHANNEL BLOCKERS	"-DIPINE"	↓SVR	PERIPHERAL EDEMA *GINGIVAL HYPERPLASIA
ARTERIAL DILATOR	HYDRALAZINE	↓SVR	SLE TACHYCARDIA
VENOUS DILATOR	ISMN ISDN NITROPRUSSIDE	↓PL	HEADACHE CYANIDE

Figure 6.5: Visualizing Antihypertensives Another Way

This was the first version of Dr. Williams's organization of medications, focused on the mechanisms or systems they influence. This does work well. If this feels better than the MAP equation, you can take it. It doesn't line up well with actually treating patients, but it is mechanistic.

Super Potent, Special Mention, Okay to Use, but Not Routine

Minoxidil (the same thing used to regrow hair) causes the opening of potassium channels in smooth muscle cells, leading to hyperpolarization, reduced calcium influx, and subsequent relaxation. If you start messing with the polarization status of excitable cells, you better know what you're doing. You should recognize this drug as a stupid-potent arterial vasodilator, a mega-upgrade to hydralazine, used to replace hydralazine when it fails to control blood pressure at max doses. Used by nephrologists and cardiologists in patients on their fifth and sixth antihypertensive, we wanted you to see it, to know about it, to know that you could continue it if the patient on it came to your service—but also to identify it as something you shouldn't be starting on your own.

Ancient, Should Not Use

Clonidine is a bad drug. Like super bad. It stimulates α_2 receptors. When it was the only medication we had, it was the only medication that worked. The oral form is taken three times a day. The problem is that if you miss a dose, the blood pressure rebounds higher than if you weren't on it at all. Now we have clonidine patches—an easy way to wean people off clonidine. Clonidine causes sedation and rebound hypertension. Its rapid-on effects make it a staple for emergency departments and urgent care. You should almost never use clonidine.

α-Methyldopa is also an α_2 receptor agonist. Previously, it was the go-to antihypertensive agent for pre-existing hypertension in pregnant women because it was the only medication (besides labetalol) thought to be safe in pregnancy. There is no other reason to consider α-methyldopa, and many studies are determining that other medications are safe in pregnancy. It, like hydralazine, can cause drug-induced lupus. You should almost never use α-methyldopa.

Ancient, Do Not Use, Ever

Reserpine and guanethidine. LOL. You have seen their names. Their historical insignificance is perpetuated here. They mess with the brain, norepinephrine vesicles, and amine release—all with the intention of lowering blood pressure. We have MAOIs, SNRIs, and SSRIs, drugs that mess with the brain, but those are reserved for treating disorders of the brain—psychiatric disease. Never mention, never suggest, and definitely never use reserpine or guanethidine.

Not Antihypertensives

You will see the **α_1 antagonists** you saw in General Pharmacology again in Renal. They are used to dilate the ureters and urethra and are useful in the management of benign prostatic hyperplasia (BPH) and as adjuncts for medical expulsive therapy in kidney stones. Their side effect is orthostatic hypotension. Terazosin is the drug you should use to treat BPH to avoid the unwanted side effect of orthostatic hypotension (see Dr. Williams's rant).

The **nondihydropyridine calcium-channel blockers** (verapamil and diltiazem) are not antihypertensives, and they are not anti-anginals. They do not show the mortality benefit of β-blockers in coronary artery disease or heart failure. They do cause the same drop in contractility as β-blockers, so they should be avoided in treating tachyarrhythmias in the setting of acute congestive heart failure exacerbation when there is a low ejection fraction. But they are excellent rate-control agents without the other side effects of β-blockers because they only affect the pacemaker cells. If someone is hypotensive because their heart rate is so fast that it can't fill, you give diltiazem intravenously to slow the heart rate down, restoring diastolic filling and improving the blood pressure. You will NOT worsen hypotension; you will FIX the tachycardia.

Choosing the Right Regimen

Remember, this is super-high level. There are many intricacies, minor side effects, and other reasons, like dosing frequency and patient preference. This is not coaching you in clinical practice. This is giving you a taste. It's ACE or ARB, never together.

DIAGNOSIS	WHAT TO START FIRST
Heart failure with reduced ejection fraction	Metoprolol or carvedilol ACE or ARB
Coronary artery disease	Metoprolol or carvedilol ACE or ARB
Diabetes with microalbuminuria	ACE or ARB
No comorbid condition	ACE or ARB or CCB or Thiazides
Chronic kidney disease not stage 4	ACE or ARB

IF THEY'VE GOT	THINK TWICE BEFORE STARTING
Diabetes with hypoglycemia risk	β-blockers
CKD-4	ACE or ARB
Angioedema (or if it was ever considered)	ACE (start the ARB instead)
Hyperuricemia or gout	Thiazides
Pancreatitis history	Thiazides
Hypertriglyceridemia	Thiazides

Citations

1. Katzung. 2018. *Basic & Clinical Pharmacology*, 14th ed., p. 187.